Angioimmunoblastic T-cell Lymphoma (AIL-TCL) Following Macrolide Administration

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Abstract

Angioimmunoblastic Lymphadenopathy with Dysproteinemia (AILD) is a rare benign reactive process which often follows exposure to certain drugs such as penicillin. Treatment with corticosteroids usually reverses the process, however there have been reports of 18% of cases evolving into non-Hodgkins lymphoma. In our case report, we present a relatively healthy woman with history of various drug hypersensitivities who developed AILD and resultant lymphoma after treatment with azithromycin.

A review of the literature has failed to find reports of AILD following macrolide exposure. Clonality, not present in other forms of hyperplasia, is present in AILD and immunosuppression may account for this difference. It is difficult to say whether the drugs are simply coincidently associated or actually cause, maintain, or exacerbate clonality in AILD and facilitate malignant transformation.

Introduction

Angioimmunoblastic Lymphadenopathy with Dysproteinemia (AILD) is a rare benign reactive process which often follows exposure to certain drugs such as penicillin. It is characterized by generalized lymphadenopathy, hepatosplenomegaly, and constitutional symptoms. Laboratory abnormalities include derangements in blood counts and a polyclonal gammopathy. Hemolytic anemia and morphologic bone marrow change are sometimes seen. Treatment with corticosteroids is typically successful in reversing the process however there have been reports of 18% of cases evolving into non-Hodgkins lymphoma. Evidence of clonality with subsequent malignant transformation suggests a possible explanation for drug association with AILD. We report a case of angioimmunoblastic lymphadenopathy without dysproteinemia evolving into T-cell lymphoma following macrolide administration.

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Case Report

History of Present Illness:

This 67y/o Japanese woman, with history of allergic rhinitis and hypothyroidism diagnosed two months prior to admission, was hospitalized one month prior to admission for new onset congestive heart failure and atrial fibrillation with rapid ventricular response. During this hospital stay, bilateral mastitis was noted with associated tender axillary adenopathy and treated with azithromycin. These resolved but follow-up two weeks later revealed generalized lymphadenopathy and biopsies of left anterior cervical and right inguinal nodes were taken. The local pathologist reported an abnormal immune reaction versus Hodgkin's and the specimens were sent to Stanford University for an opinion. Throughout this time the patient continued to suffer nausea, fatigue, appetite loss, and a slight nonproductive cough and on the day of admission felt extreme chills, shakes, and diaphoresis. She denied chest pain, shortness of breath, headache, dizziness, photo- or phonophobia, constipation, diarrhea, or symptoms of urinary tract or upper respiratory infection.

History:

No other medical or surgical history was significant. The patient was allergic to amoxicillin, cephalexin, and donnatel with reactions ranging from rash to difficulty breathing. She was on Synthroid, Lasix, Digoxin, Plavix, and Cardizem. Family history was unremarkable except for her father who died of liver failure. She did not have any tobacco, alcohol, or drug use, and denied travel and exposure to animals or chemicals. She had up-to-date immunizations and had received BCG vaccination, although her PPD was negative. Recent mammogram was negative.

Physical Examination:

On exam, temperature was 105.2° and blood pressure was 143/63. Left nostril occlusion was present with mucus and serosanguinous drainage but without septal deviation and the oropharynx was moist but erythematous without exudate. Diffuse, mobile, rubbery lymph nodes 1-3 cm which were nontender and non-fluctuent were noted especially in the right submandibular region. Neck was supple without jugular venous distention. Lungs were clear except for slight crackles and decreased fremitis in the right base. Breasts were within normal limits. Heart was tachycardic and an S4 with grade II/VI systolic ejection murmur was present at the base. Mild hepatosplenomegaly was present. No fecal occult blood was noted. Good distal pulses and no clubbing, cyanosis, or edema were present in the extremities.

Laboratory Findings:
Laboratory investigations showed a white count of 12.1, 28% bands, and 12% monocytes. Hemoglobin and hematocrit were 10.4 and 30.7 respectively and electrolytes were normal except for bicarbonate at 31. Blood urea nitrogen and creatinine were 27 and 1.2. Urinalysis contained 2+ blood and trace protein. Chest films showed diffuse bilateral infiltrates at the bases while electrocardiogram confirmed sinus tachycardia and revealed left atrial enlargement and premature ventricular contractions. A "fever of unknown origin" work-up was performed with negative blood cultures & serologies and thyroid stimulating hormone was within normal limits. C-reactive protein was 6.5.

Hospital Course:
Throughout her course, serologic studies, cultures, and immunoelectrophoresis continued to be unremarkable. Patient's condition improved slightly with empiric trovofloxacin but then deteriorated into a sepsis-like picture on the third hospital day. The patient needed to be transfused. Marrow aspirate showed only hyperplasia of megakaryocytes. Preliminary node biopsy results from Stanford suggested AILD and prednisone was initiated at 40mg BID and most of her symptoms rapidly diminished. She continued to have residual right submandibular lymphadenopathy. On day 12, routine exam revealed a 3x2cm erythematous mass causing slight nasal septal deviation and head CT and MRI showed an infiltrating left nasal lesion which had biopsy findings consistent with lymphoma. Chemotherapy with Cytoxan and vincristine resulted in regression of the lesion.

Discussion

First recognized by Flandrin and Westerhausen,[1,2] angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), a term coined by G. Frizzera in 1974,[3] is a rare benign reactive process with a lymphoma-like presentation characterized by generalized lymphadenopathy, nontender hepatosplenomegaly, and constitutional symptoms. It was Lukes et al., however, who proposed that AILD was associated with both benign and malignant forms.[4] For the purposes of this discussion, AILD, immunoblastic lymphadenopathy (IBL), and lymphogranulomatous X (LgX) have been considered one entity, AILD (their differences are noted on table II).

Clinical Features
Generalized lymphadenopathy is the *sine qua non* of AILD and these nodes often rapidly develop into soft, variably tender, movable, but not matted masses, measuring 2-3cm. Fever occurs in two thirds and chills, night sweats, malaise, anorexia, and weight loss give clue to the systemic nature of this entity. Peak incidence occurs in the seventh and eighth decades. A prodrome of maculopapular rash can be seen, without preferential location, in more than a third of patients.[5] It is commonly pruritic and follows administration of drugs such as penicillin.[2,6-8] Men are slightly predisposed, with a 1.2:1 ratio.[5]

Clinical Findings at Presentation[9-14]

Findings	% Patients
Lymphadenopathy	100
Generalized	81
Localized	21
Organomegaly	
Liver	73
Spleen	63
Fever	74
Pruritis	48
Skin Rash	45

Laboratory findings
In AILD, normochromic, normocytic anemia, particularly Coombs-positive and hemolytic, can be evident. Leukocytosis and eosinophilia may also complicate the picture. Dysgammaglobinemia, most often a polyclonal hypergammopathy, is seen in up to three-fourths of patients.[14] Low CD4 T-cell counts may be discovered during active phases of the disease.[15] An elevated lactate dehydrogenase is present in 25-85%, often with accompanying hemolytic anemia.[10,14]

Peripheral Blood Findings in AILD[9,11-13,16]

Findings	% Patients
Anemia (autoimmune)	82 (45)
Lymphopenia/-cytosis	37/5
Leukocytosis	33
Neutrophilia/-penia	26/1
Plasma cells/immunoblasts	23
Thrombocytopenia	19
Eosinophilia	18
Monocytosis	13

Serological Profile of AILD[9-13]

Findings	% Patients
Dysgammaglobulinema	
Polyclonal hypergammapathy	70
Hypogammaglobulinema	7
Monoclonal component	5
Normal gammaglobulins	23
Positive Coombs test	39

Histological diagnosis
Marked proliferation of small vessels with hyperplastic endothelium and pleomorphic infiltrate rich in immunoblasts distributed in an uneven pattern typify nodal biopsies. Pronounced and diffuse obliteration of nodal architecture can be seen, with a third of victims having some burnt-out germinal centers scattered across the field. There is often sludgy, eosinophilic material between cells. Serial nodal samples may show actual recovery of nodal architecture or

extensive fibrosis.[7] Reactive morphological changes may be seen in the spleen, bone marrow, liver, and skin but are usually less prominent. The marrow aspirate may show mild plasmacytosis or red cell hyperplasia, particularly in the setting of hemolytic anemia, but will be normal in up to half of patients.[17]

AILD is distinguished from neoplasm because peripheral sinuses and remnants of germinal centers are preserved, the angiocellular changes doe not occur with any known malignant lymphoma, and the end result in AILD is lymphocytic depletion with perivascular fibrosis not tumoral replacement of organ structures. Surgical staging is not recommended unless progression to lymphoma has occurred.[19]

Table 1.– Classification of AIL-TCL[18]

Revised European American Lymphoma (REAL) Classification	Peripheral T-cell and NK- cell neoplasm
Rappaport	Not listed (diffuse mixed lymphocytic-histiocytic, histiocytic)
Kiel	T-cell, angioimmunoblastic (AILD)
Lukes-Collins	IBL-like T-cell lymphoma
Working Formulation	Not listed (diffuse mixed small and large-cell, diffuse large cell, large cell immunoblastic)

Although rare, AIL-TCL account for 4% of all lymphomas (20% of T-cell) by Kiel classification (table I).[20] AILD-like lymphomas are surprisingly similar to IBL-like lymphomas first described in Japan.[21,22] Virtually all AILD-like lymphomas are peripheral T-cell but rare B-cell lymphomas, often EBV associated, exist.[23-27] Expanded FDC clusters & CD 21-positive reticulum cells surrounding post-capillary venules have been found to be specific for AILD-like lymphoma.[4,20]

Table 2.– Morphological Criteria: Diagnosis of AILD, Immunoblastic Lymphadenopathy (IBL), and Lymphogranulomatosis X (LgX)[3,4,9,10,12,28]

Common Findings
- Diffuse obliteration of the lymph node architecture
- Proliferation of small vessels (esp postcapillary venules)
- Polymorphous cytology
- Absence of florid germinal centres

Differences
- Immunoblasts and plasma cells are abundant in AILD and IBL; in LgX either immunoblasts, plasma cells, lymphocytes, or epithelioid cells may prevail
- In IBL, the lymph node is lymphocyte-depleted and hypocellular
- PAS-positive interstitial material is always present in IBL, but not in AILD and LgX
- Burnt out germinal centres may occur in AILD and LgX, but not in IBL

Differential diagnosis

Distinguishing collagen vascular disease, lymphoma, infection, drug reaction, and graft-versus-host disease (GVHD) from AILD is a diagnostic dilemna. Despite their shared constitutional and clinical similarities, the vasculitis, renal assault, and epidermal skin lesions that are prominent in SLE are absent in AILD.

Although malignant transformation is possible, there are several contrasts between lymphomas and pure AILD. Clinically, rarely do non-AILD-type lymphomas consistently display the generalized lymphadenopathy, hepatosplenomegaly, and constitutional symptoms which virtually define AILD. Histologically, lymphomas, with scant vasculature, have monomorphic cellularity and atypia which are features not found in AILD. Another difference are the remnant germinal centers that persist in AILD despite intense cellular proliferation.

Histologically similar, differentiating AILD from reactive processes like infections, such as infectious mononucleosis and postviral adenitis, or autoimmune disorders are important. Infections can coexist with AILD, but nodal biopsy will differentiate the two. Atypical clear cells are present in AIL-TCL, not infections.

Early AILD may have well-preserved germinal centers which may be hard to distinguish from reactive hyperplasia or Castleman's, making repeated biopsies useful. Molecular genetic analysis, with DNA hybridization, and immunophenotyping are the best techniques available for diagnosis.[13]

In many respects, GVHD is clinically identical to AILD. The generalized lymphadenopathy, hepatosplenomegaly, autoimmune hemolytic anemia, susceptibility to infection, and constitutional symptoms such as weight loss are all familiar to the GVHD picture. Skin and hepatic lesions, however, are not nearly as prominent in AILD and the history of organ transplant is noticably absent. Histologically, the immunoblast proliferation, the disappearance of follicular structures, eosinophilic deposits, and sometimes granulomatous lesions are all mutually common in the nodes and spleen of patients with both diseases. It is important to note, however, that GVHD pathogenesis is very similar to that of AILD and AILD may simply be an abnormal immune response with pharmaceutical and not tissue triggers.

Prognosis and Treatment

A stormy and unpredictable course is standard and, seemingly despite treatment modalities, a period of either rapid progression or remission occurs with fatality in months to years.[2,11,29] Death occurs in 75% of those affected with a median survival of 30 months.[30] About one third of patients respond to immunosuppressants.[13,31,32] The presence of clear cells, age of onset, type of pharmacotherapy, presence of clonality, and other factors have not been found to be good prognostic indicators for AILD.[15,33] Complete remission after steroid therapy, which occurs in up to 30%, best correlates with good outcome whereas progression to malignant lymphoma, which occur in 18-50%,[30,34] is associated with poor prognosis. Despite its "low-grade" revised Kiel classification, median survival is 16 months in malignant transformation,[23,32,35,36] with drug exposure, elevated lactate dehydrogenase, rash, and lymphocytopenia associated with more rapid progression.[30] Therapy is controversial and can be as conservative as support with steroids or as aggressive as multi-drug combination chemotherapy, utilized particularly in cases with

clonality.[10,17,37] Case reports of successful treatment of AIL-TCL by IFN-a, fludarabine, COPBLAM/IMVP-16, and 2-chlordeoxyadenosine have so far been anecdotal.[35,38-40] Infectious complications are the most common cause of fatality, especially pneumonia by CMV, *P. carinii*, and Aspergillus.[13,30,35] TMP-SMX prophylactus may be considered.

Conclusion

In 70-95%, there is evidence of clonality even in early forms of AILD, mostly in the T-cell recepter (TCR) gene.[15,24,35,41] IgH rearrangement is also present in 10% of cases.[15] Serial biopsies have shown either reduction in clones or malignant transformation.[14,23,27] Researchers theorize that the initially benign hyperplasia may simply promote clones with genetic rearrangements due to the numerous rapidly repeating cell divisions.[23] Clones, however, are not present in amounts appreciable by Southern blot assay in other forms of hyperplasia.[23] Immunosuppression in AILD may account for this difference as T-cell deficiency in regulation is known to result in B-cell proliferation and autoaggression.[5,42] The worst prognosis is for those with complex uberrant clones and chromosome 1p structural defects, which is also found in other cancers.[36]

Allergies and drugs such as aspirin, phenytoin, halothane, L-dopa, and antibiotics such as penicillins, tetracycline, and the sulfonamides have been associated previous to onset of AILD.[35,37] A review of the literature has failed to find reports of AILD following macrolide exposure. In our case report, we present a relatively healthy woman of typical age for the onset of the disorder with allergic rhinitis and history of various drug hypersensitivities.

While statistical correlation points to the strong possibility that pharmaceutical exposure may be a risk factor for subsequent development of AILD, the pathophysiologic theory of causation may be more obscure. Some evidence suggests that certain B-cell aberrations are a result of drug hypersensitivity.[4] It is difficult to say whether the drugs are simply coincidently associated or actually cause, maintain, or exacerbate clonality in AILD and if drug exposure causes AILD to be more likely to progress to frank lymphoma. Only continuing research will bring light to this query.

Figure 1.–Prominent blood vessel with extravasated blood in background of proliferation lymphosytic.

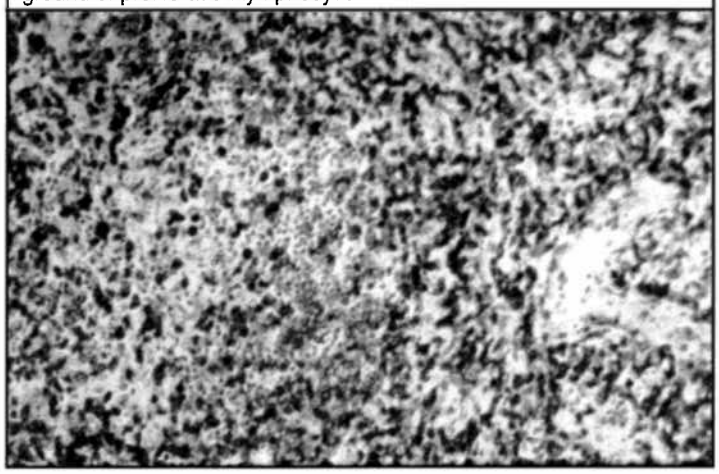
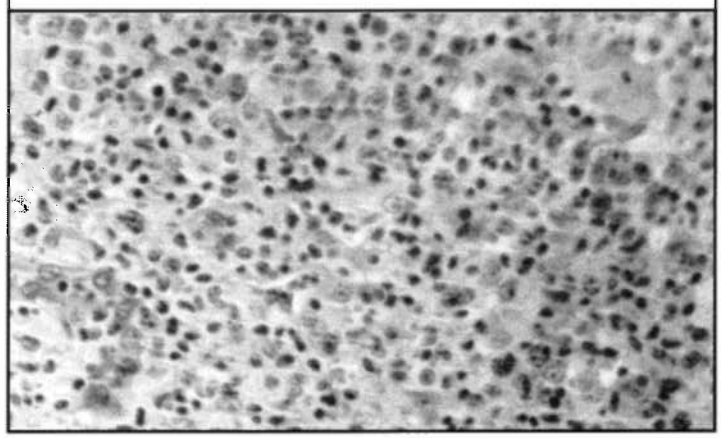


Figure 2.– High power of endothelial proliferation within lymphoma characteristic of AILD-like T-Cell lymphoma.



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References

1. Flandrin G, Daniel MT, El Yafi G, Chelloul N: Diffuse plasmacytic sarcomatoses. Actual hemat 1972; 6:25.
2. Westerhausen M, Oehlert W: Chronic pluripotential immunoproliferative syndrome. Dt med Wschr 1972; 97:1407.
3. Frizzera G, Moran EM, Rappaport H: Angioimmunoblastic lymphadenopathy with dysproteinemia. Lancet 1974; I:1070-1073.
4. Lukes RJ, Tindle BH: Immunoblastic lymphadenopathy: A prelymphomatous state of immunoblastic sarcoma.Workshop on Classification of Non-Hodgkin's Lymphomas. Univ of Chicago, IL, June 25-29, 1973
5. Knecht H: Angioimmunoblastic lymphadenopathy: Ten years' experience and state of current knowledge. Semin Hematol 1989; 26:208-215.
6. Lapes MJ, Vivaequa RJ, Antoniades K: Immunoblastic lymphadenopathy associated with phenytoin. Lancet 1976; 1:198.
7. Weisenburger DD: Immunoblastic lymphadenopathy associated with methydopa therapy: a case report. Cancer 1978; 42:2322-2327.
8. Antony AC: Allergen-associated angioimmunoblastic lymphadenopathy. Lancet 1979; 1:978
9. Lukes RJ, Tindle BH: Immunoblastic lymphadenopathy: A hyperimmune entity resembling Hodgkin's disease. NEJM 1975; 292:1-8
10. Frizzera G, Moran EM, Rappaport H: Angioimmunoblastic lymphadenopathy: Diagnosis and clinical course. Am J Med 1975; 59:803-818.
11. Flandrin G: Angioimmunoblastic lymphadenopathy: clinical, biologic and follow-up study of 14 cases. Recent Results Cancer Res 1978; 64:247-262.
12. Knecht H, Schwarze EW, Lennert K: Histological, immunohistological and autopsy findings in lymphogranulomatosis X. Virchows Arch 1985; A406:105-124
13. Ganesan TS, Dhaliwal HS, Dorreen MS, et al: Angioimmunoblastic lymphadenopathy: A clinical, immunological and molecular study. Br J Cancer 1987; 55:437-442.
14. Freter CE, Cossman J: Angioimmunoblastic lymphadenopathy with dysproteinemia. Semin Oncol 1993; 20:627-635.
15. Weiss LM, Strickler JG, Dorfman RF, Horning SJ, Warnke RA, Sklar J: Clonal T-cell populations in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. Am J Pathol 1986; 122: 392-397.
16. Pangalis GA, Moran EM, Rappaport H: Blood and bone marrow findings in angioimmunoblastic lymphadenopathy. Blood 1978; 51:71-83
17. Sallah S, Gagnon G: Angioimmunoblastic Lymphadenopathy with Dysproteinemia: Emphasis on Pathogenesis and Treatment. Acta Haematol 1998; 99:57-64.
18. Harris NL, Jaffe ES, Stein H et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994; 84(5):1361-1392.
19. Jaffe ES: Angioimmunoblastic T-cell lymphoma: New insights, but the clinical challenge remains. Ann Oncol 1995; 6:631-632.
20. Lennert K, Feller A: Histopathology of non-Hodgkin's Lymphoma ed. 2. New York: Springer-Verlag; c1992
21. Shimoyama M, Minato K, Saito H, Takenaka T, Watanabe S, Nagatani T, Naruto M: Immunoblastic lymphadenopathy (IBL)-like T-cell lymphoma. Jpn J Clin Oncol 1979, 9(s):347-356.
22. Nathwani BN, Winberg CD, Bearman RM: Angioimmunoblastic lymphadenopathy with dysproteinemia and its progression to malignant lymphoma, Surgical Pathology of Lymph Nodes and Related Organs. Edited by ES Jaffe. Philidelphia, WB Saunders, 1985:57-85.
23. Lipford EH, Smith HR, Pittaluga S, Jaffe ES, Steinburg AD, Cossman J: Clonality of angioimmunoblastic lymphadenopathy and implications for its evolution to malignant lymhoma. J Clin Invest 1987; 79:637-642.

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percentage of OPCAB patients (15.9%) had greater than 3 grafts performed compared to the traditional CABG group (14.7%).

Graft patency is an obvious important endpoint not addressed in this study. Surgeon selection bias (i.e. perhaps only patients with relatively larger target coronary vessels underwent OPCAB) also limits useful analysis. We believe that only a properly performed prospective randomized trial can adequately answer this question. Early angiographic results by others however, have been reported. Jansen et al[7] in a favorable clinical report of their first 100 patients who underwent multivessel OPCAB documented an angiographic patency rate of 95%. Calafiore and colleagues in 190 consecutive patients and Subramanian in 52 consecutive patients have reported angiographic patency rates of 98.9%,[8] and 96.2%,[9] respectively.

Not all patients can undergo OPCAB. Anatomic and hemodynamic considerations play a role as well as the experience of the surgical team. In this series, 4 patients (5.5%) initially undergoing OPCAB were converted intraoperatively to a traditional CABG. In these patients, hemodynamic instability resulted from either lifting or stabilizing the heart, necessitating conversion. There were no myocardial infarctions or other significant complications in these patients. All were discharged home safely with total hospitalizations ranging from five to nine days (mean 6.5 days). In this study, these patients were included in the traditional CABG group for analysis.

Because of these limitations, definitive conclusions regarding the role of the OPCAB in the general cardiac surgical population cannot be made. Surgeon selection bias can only be overcome with a prospective randomized clinical trial. We believe, however that these results are interesting and warrant further study. Accordingly, we have now embarked and are actively enrolling patients into a prospective randomized clinical trial comparing the OPCAB to traditional CABG. Funded by a grant from the Hawaii Community Foundation, we are studying the effects of the two procedures on neurologic function, morbidity and cost. Pre and postoperative neurologic and neurocognitive function, brain perfusion and intraoperative Transcranial Doppler analysis of cerebral microemboli, are important facets of this ongoing clinical trial.

We believe that the OPCAB is an exciting new procedure, which may have much potential. As with any new medical procedure however, careful and objective study in the context of a prospective randomized protocol should be encouraged.

References

1. Puskas J.D., Wright CE, Ronson RS, et al. Off Pump Multivessel Coronary Bypass via Sternotomy is Safe and Effective. *Annals of Thoracic Surgery.* 1998; 66: 1068-1072.
2. Roach GW, Kanchuger M, Mora Mangano Christina, et al. Adverse Cerebral Outcomes after Coronary Bypass Surgery. *New England Journal of Medicine.* 1996; 335: 1857-1863.
3. Venn G, Klinger L, Smith P, et al. Neuropsychological sequelae of bypass twelve months after coronary bypass surgery. *British Heart Journal.* 1987; 57:565
4. Smith PL, Treasure T, Newmann SP, et al. Cerebral consequences of cardiopulmonary bypass. *Lancet* 1986; 1: 823-825.
5. Rosengart TK, Helm RE, Klemperer J, et al. Combined Aprotinin and Erythropoietin Use for Blood Conservation: Results with Jehovah's Witnesses. *Annals of Thoracic Surgery.* 1994; 58:1397-1403.
6. Hammon JW, Stump DA, Kon ND, et al. Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. *Annals of Thoracic Surgery* 1997; 63:1613-1618.
7. Jansen EWL, Borst C, Lahpor JR, et al. Coronary artery bypass grafting without cardiopulmonary bypass using the Octopus method: results in the first one hundred patients. *J Thorac Cardiovasc Surg* 1998, 116, 60-7.
8. Calafiore AM, Giammarco GD, Teodori G, et al. Midterm results after minimally invasive coronary surgery (LAST operation). *J Thorac Cardiovasc Surg* 1998, 115 763-71.
9. Subramanian VA. Less invasive arterial CABG on a beating heart. *Ann Thorac Surg* 1997, 63:S68-71.

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24. Feller AC, Griesser H, Schilling CV, Wacker HH, Sallenbach F, Bartels H, et al: Clonal gene rearrangement patterns correlate with immunophenotype and clinical parameters in patients with angioimmunoblastic lymphadenopathy. Am J Pathol. 1988; 133:549-556.
25. Weiss LM, Jaffe ES, Lui XF, ChenYY, Shibata D, Meideiros JL: Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphomas. Blood 1992; 79:1789-1795.
26. Abruzzo LV, Schmidt K, Weiss LM, Jaffe ES, Medeiros LJ, Sander CA, Raffeld M: B-cell lymphoma after angioimmunoblastic lymphadenopathy: a case with oligoclonal gene rearrangements associated with Epstein-Barr virus. Blood 1993; 82:241-246.
27. Ohshima K, Takeo H, Kikuchi M, Kozuru M, Uike N, Masuda Y, Yoneda S, Takeshita M, Shibata T, Akamatsu M: Heterogeneity of Epstein-Barr virus infection in angioimmunoblastic lymphadenopathy-type T-cell lymphoma. Histopath 1994; 25:569-579.
28. Lennert K, Knecht H, Burket M: Vorstadien malingner Lymphome. Verh Dtsch Ges Pathol 1979; 63:170-196
29. Nathwani BN, Rappaport H, Moran EM, Pangalis GA, Kim H: Evolution of immunoblastic lymphoma in angioimmunoblastic lymphadenopathy. Recent Results Cancer Res 1978; 64:235-240.
30. Pangalis GA, Moran EM, Nathwani BN, et al: Angioimmunoblastic lymphadenopathy. Long-term follow-up study. Cancer 1983; 52:318-321.
31. Archimbaud E, Coiffier B, BryonPA, et al: Prognostic factors in angioimmunoblastic lymphadenopathy. Cancer 1987; 59:208-212.
32. Tobinia K, Minato K, Ohtsu T, Mukai K, Kagami Y, Miwa M, Watanabe S, Shimoyama M: Clinicopathologic, immunophenotypic, and immunogenotypic analyses of immunoblastic lymphadenopathy-like T-cell lymphoma. Blood 1988; 72:1000-1006.
33. Ch'ang HJ, Su IJ, Chen CL, Chiang IP, Chen YC, Wang CH, Cheng AL: Angioimmunoblastic lymphadenopathy with dysproteinemia—lack of prognostic value of clear cell morphology. AngiOncol 1997; 54:193-198.
34. Nathwani BN, Rappaport H, Moran EM, Pangalis GA, Kim H: Malignant lymphoma arising in angioimmunoblastic lymphadenopathy. Cancer 1978; 41:578-606.
35. Siegert W, Agthe A, Griesser H, Schwerdtfeger R, Brittinger G, Engelhard M, Kuse R, Tiemann M, Lennert K, Huhn D: Treatment of angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma using prednisone with or without the COPBLAM/IMVP-16 regimen. Ann Intern Med 1992; 117:364-370. *-nonrandomized*
36. Schlegelberger B, Zwingers T, Hohenadel K, Henne-Bruns D, Schmitz N, Haferlach T, Tirier C, Bartels H, Sonnen R, Kuse R, Grote W: Significance of cytogenetic findings for the clinical outcome in patients with T-cell lymphoma of angioimmunoblastic lymphadenopathy type. J Clin Oncol 1996; 14:593-599.
37. Ironside P, Cornell FN: Immunoblastic lymphadenopathy: A clinicopathological study of 16 cases. Pathology 1979; 11:27-37.
38. Kozuru M, Hashimoto M, Takahira H, Uike N, Ohoshima K, Takeshita M, Kikuchi M: AILD-like dysplasia transformed in AILD-type T cell lymphoma in an HTLV-I carrier: Usefulness of interferon-a. Acta Haematol 1996; 96:92-98.
39. Ong ST: Successful treatment of angioimmunoblastic lymphadenopathy with dysproteinemia with fludarabine. Blood 1996; 88:2354-2355
40. Sallah AS, Bernard S: Treatment of angioimmunoblastic lymphadenopathy with dysproteinemia using 2-chlorodeoxyadenosine. Ann Hematol 1996; 73:295-296
41. Takagi N, Nakamura S, Ueda R, Osada H, Obata Y, Kitoh K, Suchi T, Takahashi T: A phenotype and genotypic study of three node-based, low-grade, peripheral T-cell lymphoma: Angioimmunoblastic lymphoma, T-zone lymphoma, and lymphoepithelioid lymphoma. Cancer 1992; 69:2571-2582.
42. Kaneko Y, Maseki N, Sakurai M, Takayama S, Nanba K, Kikuchi M, Frizzera G: Characteristic karyotypic pattern in T-cell lymphoproliferative disorders with reactive 'angioimmunoblastic lymphadenopathy with dysproteinemia-type' features. Blood 1988; 72:413-421.